ANKYLOSING SPONDYLITIS AND MULTIPLE SCLEROSIS: A SURPRISING PARALLEL

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ABSTRACT

Ankylosing Spondylitis (AS) and Multiple Sclerosis (MS) are two different chronic autoimmune and inflammatory diseases, one rheumatic and the other one neurological, apparently without any connection between them. Yet a few case reports proved that AS may be associated with MS and this situation should be considered in some epidemiological environment.

Although the geographic map of incidence is approximately superposed for both entities there are only a few cases of association. Recent studies revealed that most loci associated with MS are located very close to or even within genes encoding molecules involved in immune system function, confirming the hypothesis that MS is a disease with immunologic mechanism. In addition, some of these loci are also associated at least with another autoimmune disease, thus reinforcing the idea that autoimmune diseases may have a common origin.

If MS is more common in patients with AS than in the general population, we can speculate the existence of common factors involved in these diseases. Because of the limited number of cases that associated these two diseases, the correct diagnosis of both entities considered separately or together becomes mandatory especially reflecting on the anti-TNFα agents used to treat AS which may exacerbate or induce a latent MS or demyelination processes in the central nervous system. In terms of pathogenic mechanisms, they are poorly known in both diseases, but each is characterized by an initial immune and inflammatory attack, in MS the target is the myelin sheath and in AS the enthesis tissue. A case with association between the two diseases raises important issues in choosing an appropriate treatment.

Keywords: ankylosing spondylitis, multiple sclerosis, autoimmune disease, TNFα

INTRODUCTION

Ankylosing Spondylitis (AS) and Multiple Sclerosis (MS) are two different chronic autoimmune and inflammatory diseases, one rheumatic and the other one neurological, apparently without any connection between them. Yet a few case reports proved that AS may be associated with MS and this situation should be considered in some epidemiological environment. If MS is more common in patients with AS than in the general population, we can speculate the existence of common factors involved in these diseases. There is a possible association between AS and MS in the white population. The coexistence of MS and AS has been exceptional described at a black patient. (1). Both diseases have unclear etiology and one of the assumptions is the molecular mimicry in which antigens of microorganisms are recognized as a host protein and induces the immune disease.

Clinic and histocompatibility antigens in literature there are few case reports that associate AS with MS. One case of MS after treatment with adalimumab was reported in a patient with AS HLA B27 positive. On the other hand, it was reported one case of MS-like syndrome also in a patient with HLA B27 positive AS. (2) MS has also been reported in a patient with HLA B27 negative diagnosed with AS. (3) Because of the limited number of cases that associated these two diseases, the correct diagnosis of both entities considered separately or together becomes mandatory especially reflecting on the anti TNFα agents used to treat AS which

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may exacerbate or induce a latent MS or demyelination processes in the central nervous system. The treatment for patients diagnosed with MS or with a positive family history of MS should avoid the anti TNFα agents (4-7).

One of the reported cases is HLA B 27 negative. There is a genetic geographic map profile relatively similar for the two diseases and this exception is quite unexpected. A study of 420 patients diagnosed with MS showed a prevalence of 10.2% for HLA B27 patients. About 25% of these positive patients had AS diagnostic criteria. (8) In the general population 5-6% of HLA B 27 positive individuals have AS (9,10,24).

Definitions and evolution AS is a chronic inflammatory disease with unknown etiology, from the spondyloarthropathies group, affecting musculoskeletal system mainly at the sacroiliac joints and axial skeleton, sometimes with peripheral joint involvement, with extra-articular manifestations that affects: eye, heart, lung, kidney and neurological system. The disease develops in four stages: sacroiliac, lumbar, dorsal and cervical. Evolution of AS is chronic, progressive, and in the absence of appropriate pathogenic treatment instituted early, it ends in vicious positions of the spine, deficiency in functional status, with physical disability and the occurrence of visceral manifestations that reduce life expectancy. It accompanies most common neurological disorders such as cauda equina syndrome, C1-C2 subluxation, vertebral fractures and spinal cord compression with myelopathy or monoplegia.

MS is a demyelinating disease, which is part of the inflammatory demyelinating diseases of the central nervous system with a highly complex clinical picture generating motor deficits, ataxia, oculomotricity abnormalities, sphincter disturbances, sensitivity deficits, etc. Taking into account on the evolution or clinical progression there were described in since 1966 four clinical forms of the disease. The most common (80%) is *relapsing-remitting* (RR) characterized by impredictibile attacks or relapses followed by periods of silence or absence of disease activity (remission). Neurological deficits that occur during attacks may be remitted completly or in part. Usually this subtype of disease begins as a *clinically isolated syndrome*, namely the first attack of demyelination that still does not fulfill the criteria for clinically defined disease. Between 30 and 70% of patients with clinically isolated syndrome will develop MS later. (11) The *secondary progressive* type refers to patients who initially evolves with attacks (65% of patients with RRMS) and then will present a continued neurological degradation without periods of remission (12). The *primary progressive* (PP) type occurs in 10-20% of individuals and the evolution is progressive from onset, without remission or minor remissions after initial symptoms. The rarest type is the *progressive relapsing* which is common in patients with a stable rate of degradation from onset but also have clear superimposed attacks (13).

HISTORY AND COMMON MEDICAL CELEBRITY

Even if there is an old history of the two diseases, the evidences that reveals the association between AS and MS are relatively recent. The study of Ramses II mummy (2900 BC) proved suggestive changes of AS ossification of the spine. The first written story about the disease dates back to 1559, when Realdo Colombo describes the typical abnormalities in two skeletons (14) and in 1693, Bernard Connor describes characteristic changes with ilium, sacrum, lumbar and part of thoracic spine fused in a single bone. (15) Later in 1850 Brodie describes the case of a 31 years young man suffering from vertebral ankylosis who associated "severe inflammation of the eye." In 1884 A. Strumpell reports two cases with complete ankylosis of the spine and the hip joints. Detailed descriptions of the disease belong to von Bechterew (Russia, 1893) and Pierre Marie (France, 1899). They gave the name of the disease known at the time: Bechterew disease, Strumpell Marie desease or Strumpell-Marie-Bechterew morbus. From 1930 Krebs, Scott, Robert and Forestier defined radiologic characteristical sindesmophytes, sacroiliitis (16,17,18).

In 1974 Moll introduces the concept of spondylarthropathies and AS is the first representative desease of this group (19,20).

Among the first patients that were identified in the literature who may have had MS is a Dutch-born nun, saint Lidwina of Schiedam (1380-1433). Starting from age 16 until the end of her life she suffered intermittent pain, weakness of the lower limbs and intermittent loss of vision, typical symptoms of MS (21). Another possible case of MS is a young woman named Halldora who lived in Iceland around 1200 who suddenly lost her vision. After praying to saints for 7 days the vision came back. Both cases support the "Viking gene" hypothesis in the spread of this disease (22).

The great French neurologist Jean-Martin Charcot (1825-1893) was the first author who described the disease as a separate entity. He named the dis-

ease "sclerose en plaques" and considered that it was characterized by the triad: intentional tremor, nystagmus and telegraphic speech (23).

Interestingly the identification of AS, a rheumatologic disease, involved two neurologists: the german doctor Adolph Strümpell (1853-1925) who has contributed to the description of hereditary spastic paraplegia Strümpell-Lorrain and french physician Pierre Marie (1853-1940) who is associated with description of hereditary motor and sensory neuropathy Charcot Marie Tooth.

GEOGRAPHICAL SPREAD AND GENETICS

AS is spread across the globe, and it's affecting all ethnic groups. The incidence is estimated at 7.3 per 100,000 population per year. The prevalence of the disease is 0.5-2% and is correlated with the prevalence of HLA-B27 subtype. In the general population 5 to 6% of positive HLA B27 adults develop disease wich is significantly more common in first-degree relatives HLA B 27 positive of the AS patients (24). About 10-30% of the offspring of patients with AS have signs and symptoms of disease. HLA B27 molecules are present in 80-98% of Caucasian SA patients in contrast to only 8% in the general population. The frequency of HLA B27 is up to 18% in populations of Northern European, Scandinavian, 14% at Basque population and is lower in Southern European countries (6%), Western Europe (7%), India (2-6%), Armenian, Iranian and israilien population (3-5%). In contrast in black Africans and Japanese the prevalence of HLA B 27 is below 1%. There are 23 subtypes of HLA-B27, encoded from B*2701 to B*2723. The subtype B *2706 is specifically associated with spondiloartropathies and and subtype B *2709 with AS (25,26).

MS is prevalent in the northern hemisphere and the prevalence rate is from 0.5 to 1.5 per 1,000 inhabitants. The disease is more common in Caucasian individuals. The highest prevalence is found in northern European countries. The population with a family history of MS has a 2-4% risk of developing the disease in their lifetime compared to 0.2 in the general population. Researches have shown that risk of the relatives of patients with MS is high mainly due to genetics and less due to similar lifestyle. However the influence of environmental factors such as infections with Epstein Barr or vitamin D influences the incidence and this is demonstrated by numerous studies. MS is strongly associated with HLA DR2 and also with allele type DRB1 *1501 whose frequency is 3-20% in the European population with an increase from south to north (27).

Both AS and MS have some degree of genetic predisposition, most important in AS. Recent studies proved that most loci associated with MS are located very close to or even within genes encoding molecules involved in immune system functioning, confirming the hypothesis that MS is a disease with immunologic mechanism. In addition, some of these loci are also associated at least with another autoimmune disease, thus reinforcing the idea that autoimmune diseases may have a common substrate. Available data suggest that in pathogenic autoimmune diseases there is a group of genes associated with all or the vast majority of disease genes plus specific ones for each disease. The existence of this partial common genetic platform for autoimmune diseases may explain some of the similarities between MS and AS (28).

ENVIRONMENTAL FACTORS

For both diseases there are some studies supporting a possible involvement of environmental factors in pathogenic mechanisms, particularly infectious factors. Elevated serum levels of IgG and IgA Ac anti polysaccharides belonging to Klebsiella pneumaniae identified in patients with AS were an argument for the intervention of environmental factors. Arthritogenic peptide hypothesis was formulated as trigger events in the pathogenesis of AS, and also of reactive arthritis, which is part of the same large group of spondylarthropathies and in wich there is documented a presence of DNA, RNA and bacterial proteins in the affected joints (29).

Correlation between AS and subclinical forms of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease and intestinal flora intervention represented by Enterobacteriaceae, Bacteroides and Bifidobacteriium suggests that in AS pathogenesis the immune response is reacting against intestinal bacteria (30).

Smoking increases the risk of MS in a dose dependent manner. Some studies have shown that smoking is correlated with the progression and severity of disease and with the risk of conversion to secondary progressive form (31).

Infectious factors have been incriminated in causing MS and perhaps there are some microorganisms that can cause the disease in individuals with genetic susceptibility but have not yet been identified pathogens that increase, decrease or not affect the risk of MS. Recent animal studies suggest that commensal intestinal flora could be essential in triggering the immune process in the absence of pathogens. Epstein Barr virus is an infectious

agent associated with risk of MS. Patients who are seronegative for Epstein Barr have a very low risk of developing the disease compared to positive ones (99% of MS patients are seropositive compared with 95% in the general population) (32).

The moment of exposion to environmental factors has an important role in MS, children and adolescents being the most vulnerable. Migration studies have shown that there are high-risk areas and low risk areas and individuals who will migrate before adolescence would have the risk of the destination area and those who emigrated after the teenager will keep risk from home (33).

MS risk may be influenced by month of birth. In the Northern Hemisphere, the highest risk is for those born in May and the lowest for those born in November suggesting that the influence of environmental factors on pregnancy could have consequences later in life (34).

Other environmental factors that might be associated with MS are exposing to toxins, especially the solvents. Immunizations were discussed but there is no conclusive evidence to support their role in MS. Hormonal and dietary treatments were also evaluated but it could not be establish a clear link between them and MS (35).

On the other hand it was observed that serum levels of uric acid are lower in MS patients than in the general population. Also MS patients have a lower incidence of gout and was released the assumption of the protective role of uric acid but without a definite conclusion until now (36).

PATHOGENY

The mechanisms underlying the occurrence of the AS remain partially known but a number of characteristics of the disease are unanimously accepted, including increased serum levels of acute phase reactants, inflammatory histology and immune mechanisms involving close association with HLA B27. The peripheral blood of patients and healthy subjects who are HLA-B27 positive have low levels of T lymphocytes secreting TNFα and IFN-γ compared to subjects with negative HLA B27. Instead, there is excess production of IL10 by CD8 + T lymphocytes. Both of these abnormalities are partly explained by the existence of the TNF-308 gene polymorphism (37).

Overexpression of TNFα in the sacroiliac joints confirmed its role in explaining the cascade of cytokines involved in inflammation and the therapeutic effect of TNFα blockers in Th1 anomaly correction (38). Cascading pathogenic mechanisms involve Th17 subset produced by participation IL 12 implicated in Th1 differentiation of naive lymphocytes and IL 23, responsible for the expansion of Th17 lymphocytes. The Th17 subset has the main function of IL17 production that has a pathogenic involvement both in AS and in psoriatic arthritis and Crohn's disease (39). The way each of these cells or cytokines are involved in the pathogenic mechanism of AS is incompletely known. Histopathological lesions show that AS pathogenic process follows three stages: **inflammation** – responsible for the erosions of the cartilage and subchondral bone damage, **the repair process** – characterized by the appearance of fibrous tissue and fibrous structures, and **bone formation** – sindesmophytes development.

Inflammation. The entheses, which are insertions of a tendon, ligament, capsule, or fascia into bone, are the first immune and inflammatory target in AS. Also the sacroiliac joints, the peripheral joints synovia and the intervertebral discs are involved. Autoreactive T cells are activated by an external bacterian antigen and then recognise endogenous peptides presented by HLA-B27. The microbes or antigen-specific T cells might be transported to the entheses and cause inflammation (40,41).

The inflammated tissue is infiltrated with T cells (CD4+ predominates over CD8+), B cells (CD20+ and macrophages CD68+) and characterised by the overexpression TNFalpha and TGFbeta. The association between HLA B27 and AS is explained by the role of CD8 + T cell which recognizes an "arthritogenic" self-peptide presented by HLA B27. TGFβ may provide a protection during the early inflammatory process but also induces non-specific fibrosis.

The repair process is characterized by synovitis and myxoid bone marrow with formation of pannus and granulation tissue. These processes destroy and then replace articular cartilage and subchondral bone. The cellular infiltrate is composed of CD68+, CD4+ T cells, macrophages, B cells, and NK cells. The inflammatory fibroblast cells infiltrates the bone adjacent to the entheseal tissue and also invades the subchondral bone. An important role has the capillary invasion from bone marrow. TGFβ has also a role in formation of a new fibrous scar cartilage. Overexpression of TGFβ and bone morphogenic proteins (BMPs) may induce disc degeneration (42,43).

Bone formation. The repair process is followed by endochondral ossification and bone ankylosis. Newly formed cartilage and the previous one are

transformed in bone tissue and the bone is fused (44). The ankylosis process might be initiated by the mechanical forces and mediated by the bone morphogenetic proteins and TGFβ. TGFβ and BMPs play also a role in ossification processes. The BMP 6 transgenic mice develop florid periostitis so this cytokine may be important in new bone formation (45,46).

The pathogenesis of MS is also based on inflammation and immune mechanisms and it is characterized by inadequate stimulation of the immune system wich will cause a cascade of biological events starting with focal lymphocytic infiltration and activation, activation of oligodendrocytes, demyelination and remyelination, axonal degeneration and gliosis.

Inflammation. Infiltration and activation of immune cells in the CNS (T lymphocytes, monocytes and other immune cells) have an important contribution in the initiation and maintenance of the inflammatory process.

Crossing the blood-brain barrier by immune cells is a crucial moment in triggering multiple sclerosis. This moment is favored by interaction with integrins, cell adhesion and P-selectin CAM1, VCAM-1. Another important event is the binding of the lymphocyte integrin α4 β1 (VLA-4) to VCAM-1 on thebrain vascular endothelium; blockade of this binding by the humanised monoclonal antibody natalizumab has a potent therapeutic effect in relapsing MS (47).

The leading role in driving inflammation in MS is granted by different types of T lymphocytes wich are activated by antigen-presenting cells (APC). Thus, CD4 + lymphocytes are activated by specialized APCs (macrophages, B cells) via MHC class II and lymphocytes CD8 + will be activated by non specialized APCs (oligodentrocite neurons) via MHC class I. A particular subset of CD4 + cells secreting interleukin 17 (Th17 cells) may interact with neurons independently by MHC. The role of Th17 cells is underscored by the encouraging results obtained in phase II studies with secukinumab, an antibody that blocks the activity of IL-17. Contribution of CD4 + prevails over the CD8 + cells wich can have immunoregulatory role (48).

Macrophages represent another major player in orchestrating the immune attack on myelin and axons in the CNS. They come either from the activation of resident microglia in the CNS parenchyma or from peripheral circulating monocytes recruitment. Activation of microglia/macrophages is achieved either by release of proinflammatory cytokines such as IFN-γ and TNFα by activated T lymphocytes or by myelin degradation products. There are two types of macrophage, M1 with proinflammatory phenotype and M2 with immunomodulatory role that facilitate CNS repair (49).

B lymphocytes are also involved in the pathogenesis of MS. They act as antigen-presenting cells and as a source of autoantibodies against CNS structures. Discovering the follicular type aggregates of B lymphocytes in the meninges of patients with SMSP support their pivotal role in mediating the gray matter lesions (50).

On the other hand, it has been found that the use of anti-CD-20 monoclonal antibodies (specific B-cell antigens) such as rituximab had a beneficial effect on inflammatory activity in MS (51).

From the immune response to pathology. Immune cells can cause tissue destructions through direct or indirect mechanisms. After activation cytotoxic T cells release pro-inflammatory cytokines such as interferon-γ, TNFα, perforine, granzymes A and B. TNFα can trigger cell death via the p55 receptor on neurons and silencing of survival signals (52). IFN-γ increases glutamate neurotoxicity and calcium influx into neurons through binding to the IFN-γ receptor and modulating the IFN-γ/AMPA GluR1 receptor complex, which leads to dendritic-bead formation and consequently to cell death (53). Perforin and granzymes directly damage the membrane and cause a sodium and calcium influx that ultimately leads to energy breakdown in the cell. The interaction of the Fas-antigen on CD8+cells with the Fas-ligand (FasL) on neurons is a further mechanism that activates the intracellular caspase cascade and causes axonal/neuronal damage (54). Activated microglia may contribute directly to the formation of lesions by releasing myeloperoxidase, reactive oxygen species and proinflammatory cytokines (interferon γ as TNFα, IL-1 and 6) (55).

Neurodegeneration. Axonal degeneration is caused by mitochondrial dysfunction induced by reactive oxygen species and nitric oxide produced by activated microglia and infiltrating macrophages. Decreased mitochondrial activity due to oxidative stress leads to reduced production of ATP. In parallel energetic needs increase due to reorganization of ion channels along demyelinated axolema. This energy imbalance will disrupt the activity of ion pumps resulting in massive accumulation of intracellular calcium and activates harmful lipases and proteases leading ultimately to cell death (56).

Neuronal energy deficit, coupled with inflammation, reduce the pH of the cell and determines prolonged acidosis wich will induce axonal degeneration by activating the acid-sensitive ionic channel 1A (ASIC) (57).

The release of iron from dying oligodendrocytes will amplify neurodegeneration by potentiating the harmhull effect of reactive oxygen species on the tissues (58).

In MS the extracellular glutamate concentration is high due on one hand to increased release from macrophages and activated microglia and on the other hand to decreased degradation by oligodendrocytes. Excessive glutamate will disrupt intracellular ion homeostasis favoring the accumulation of intracellular calcium and activation of calcium-dependent enzyme leading to cell death (59).

Demyelination and remyelination. Demyelination occurs both in the white and gray matter. Acute demyelination is thought to be primarily responsible for conduction blocks that cause acute neurological deficits. In addition, demyelinating axons may become hyperexcitable and generate spontaneous impulses that translate into positive symptoms.

Remyelination is favored by M2 microglia wiche stimulate oligodendrocyte precursor proliferation. Remyelination contributes not only to clinical remission but also to the long-term protection of the axon (60).

Gliotic response consists in hypertrophy and proliferation of astrocytes in inflammatory demyelinating lesion edge and is secondary to neuronal injury and apoptosis of oligodendrocytes. Reactive astroglial cells are traditionally viewed as having harmful consequences for axonal survival, through changes in the environment and release of toxic factors and glutamate-mediated excitotoxicity, and might limit the repair mechanism of remyelination. Astrocites proliferation is an early event in MS and the combined presence of axonal damage and gliosis is important in disease progression (61).

AGE OF ONSET AND PREDICTIVE FACTORS FOR SEVERE DISEASE

AS generally begins at a young age in males in the second or third decade of life (62,63). Age of onset is in the range of 15-40 years in 90% of cases. (64) The disease affects males 2-3 times more frequently than women, 65-80% of cases diagnosed with SA being male. Women seem to have a later age of onset and more peripheric manifestations then man (65,66). The progression of disease is strongest in the first 10 years (67).

Mortality is increased in patients with AS and circulatory disease is the most frequent cause of death (68).

Male gender and one of the following in the first 2 years of disease: erythrocyte sedimentation rate (ESR) > 30 mm/h, unresponsiveness to NSAIDs, limitation of lumbar spine, sausage-like fingers or toes, oligoarthritis and onset < 16 years are predictive factors for severe AS and severe outcome (69,70).

Average age of onset of MS is between 29-32 years and disease predominates in women in a cumulative rate of 1.77 to 1. Peak age is 5 years younger in women and the onset of the disease may lie in the second decade. Approximately 5% of cases begins before 18 years. MS is a debilitating disease of young adults. The average age of death is 58.1 years compared to 70.5 for all deaths. MS patients can survive through 82% of total life expectancy (71).

RELAPSES VERSUS FLARES

Over the course of AS there are two types of flares: localized and generalized. Flares are not as relevant and obvious like in MS. Localized flares in AS are described as emphasizing pain and reduced mobility in a region of the spine, with relatively minor symptoms (fatigue or stiffness), while generalized flares involving severe pain and severe reduction of mobility, which adds marked systemic symptoms (sweating, fever, flu-like symptoms, tiredness and symptoms of depression). Flares can last from days to weeks (72). There are evidences that patients who have major flares have also higher levels of disease activity during flare-free periods comparing with those who have no major flares (73).

In MS an attack is defined as an acute or subacute type of clinical dysfunction that reaches its peak in a few days or weeks followed by full or partial remission of these dysfunctions. The minimum duration is 24 hours and is set arbitrarily. An attack is associated with appearance of new lesions or extension of the old ones. There are also pseudoattacks that occur when the patient develops a fever, infection, physical activity or metabolic dysfunction (74).

OCULAR DAMAGE WITH DIFFERENT TISSUE TARGETS

Both AS and MS have ocular involvment but the tissue tergeted is different. Of extraarticular manifestations: eye, heart, lung, renal, neurological, AS is associated with a high frequency of 25-30% of cases with acute anterior uveitis or iridocyclitis. Pa-

tients may have unilateral eye pain, photophobia, tearing, congestion, ocular symptoms occurring in attacks lasting 4-8 weeks. Sometimes damage is recurrent and bilateral (75).

Acute anterior uveitis is very common being present in 95% of patients with AS HLA B27 positive. Also there are evidences that there is a similarity between the genes involved in AS and in acute anterior uveitis, and some genes are independent risk factors for acute anterior uveitis (76). Visual evoked potentials are delayed in patients with SA and a possible diagnostic of MS should be considered in this cases (77,78).

Optic neuritis (ON) in MS is acute or subacute and consists of eye pain on eye movements accompanied by varying degrees of vision loss, especially in central vision. Visual field examination identifies a central scotoma. After an attack of ON approximately 90% of patients becomes normal after 2-6 months. Uhthoff phenomenon appears when body temperature rise and consists of „visual blurring" (79).

NONRADIOLOGIC SACROILIITIS AND ISOLATED RADIOLOGIC SYNDROME

MRI techniques can identify inflammatory activity in the spine and sacroiliac joints long before the appearance of structural lesions visible on conventional radiographs. Use of fat suppression T2 sequences, FSE (fast spin echo), STIR (your shor inversion recovery) after administration of Gd-DTPA paramagnetic contrast (gadolinium – diethylenetriaminepentaacetic acid) has a high sensitivity in detecting permeability and increased tissue perfusion characteristic of acute inflammation. The presence of fatty lesions or a combination of inflammation and fatty is a strong predictor of radiographic spinal progression (80,81). The possibility of very early detection of acute inflammatory phenomena led to the development of the concept of non-radiographic axial spondyloarthritis (82).

Radiologically isolated syndrome, a concept introduced by Bordett (2009), Lebrun (2009) and Miller (2008) describes a subset of individuals without clinical or neurological events but with pictures suggestive of demyelination. The risk of conversion to CIS is 34% in the next five years (83).

TREATMENT

Although in recent years great efforts have been made to treat AS, there is no known cure for this disease. Currently, treatment of pathogenic include:

– NSAIDs: non-selective, selective COX-2 and coxibs – associated with a good response and considered more efficient in this desease then in other chronic rheumatologic inflammatory entities

– Disease Modifying Antirheumatic Drugs-DMARDs – immunosuppressive drugs. This type of medication, used in forms with peripheral manifestations is interfering with the pathogenic mechanisms of the disease but their potential to stop disease progression is very low and that's why their use became limited (84).

– Biological therapy – studies from even about 14 years ago (85) have shown that biological TNFα blokers significantly reduced disease activity, improved clinical status and quality of life, and especially have a role in reducing radiological progression. Treatment with anti TNFα is a major step forward in the management of rheumatic diseases but this therapy is associated with numerous side effects. In addition to infectious complications, another category of undesirable reactions is the appearance of central nervous system demyelinating diseases such as multiple sclerosis, optic neuritis, myelitis. There are reports proving CNS demyelination, Miller Fisher syndrome, Guillain-Barré syndrome leukoencephalopathy, polyneuropathies associated with TNF α blokers (86-92).

In the last years efforts have been made to discover new therapeutic strategies in MS that provide greater satisfaction, an improved compliance and adherence of patient to treatment. One of the options was to explore oral route and to investigate the efficacy and safety of oral therapies for MS wich are already used for other autoimmune diseases. Fumaric acid esters (FAE) are used for treatment of systemic psoriasis for over 40 years and clinical trials have demonstrated a good efficacy and safety profile (93).

Based on similarities in the inflammatory cascade of psoriasis and MS, researchers hypothesized that FAEs may also have beneficial effects in MS. This hypothesis became stronger with the accidental observation of MS symptom relief and disease stabilization in patients treated with oral fumarate for concomitant psoriasis. The phase II and III trials recently confirmed a favorable balance between efficacy, safety and tolerability of oral fumarate in the treatment of RRMS (94).

Current treatment of MS cu includes four lines of medication. It is important to treat as soon as in the "therapeutic window" starting with clinically isolated syndrome. The first line includes beta interferons, glatiramer acetate, teriflunomide, dimethylfumarate. In some countries including Unit-

ed States fingolimod is accepted as part of the first line. In case of suboptimal response changes can be done between interferons and glatirameracetat or can move to the second line which include fingolimod, natalizumab and alemtuzumab. One should note the existence of a stratified risk related to the possibility of developing progressive multifocal leucoencephalopathy, a phenomenon predicted by the presence of JC virus in CSF (95,96).

If the new response is also suboptimal then can be used the third line comprising Mitoxantrone or Cladribine. We should be carefully because administration of immunosuppressive therapy as add-on therapy for first line compromises future use of natalizumab. If a new type of suboptimal response appear than someone can proceed to the 4th line treatment comprising marrow transplantation.

Attacks receives treatment with methyl prednisolone 3-5 or even 7 days. The clinical and MRI examinations can define the stop of disease progression and the patient can be declared as responder (97).

Drugs included in Modifing Disease Treatment group meet the most favorable effects in patients with RRMS. A limited number of patients with SMSP react favorably to beta interferons 1b and 1a administered 3 times per week.

INSTEAD OF CONCLUSIONS

MS and AS are both chronic autoimmune and inflammatory diseases. Both of them are debilitating diseases of young adults, associated with significant disability and high socioeconomic costs.

Although the geographic map of incidence is approximately superposed for both entities there are only a few cases of association.

In terms of pathogenic mechanisms, they are poorly known in both diseases, but each is characterized by an initial immune and inflammatory attack, in MS the target is the myelin sheath and in AS the enthesis tissue. Environmental factors like infectious agents are involved in both deseases.

The inflammation in MS is followed by axonal degenerative phenomena and in AS by degenerative phenomena and new bone formation. In both cases there have been done great efforts to establish early diagnosis methods. MRI is essential to confirm CIS as an early diagnosis of MS or the nonradiologic sacroiliitis in AS. MRI plays a major role in early diagnosis of each disease.

The treatment of both diseases includes biological agents. Given the possibility of worsening of demyelinating lesions following the treatment with anti TNFα agents used in AS, a case with association between the two diseases raises important issues in choosing an appropriate treatment. A related feature of anti-inflammatory treatment is poor response to corticosteroids in AS (98) compared with good response in MS. Most chronic inflammatory diseases evolve with flares and remission periods and MS is included in this pattern, but in AS this is not very typical compared to other chronic inflammatory rheumatic diseases.

More studies should be made to find an explanation for the coexistence of both diseases. However any case that associates MS with AS should be reported. Because of some common pathogenesis the association of both diseases might be more complex then we can expect.

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REFERENCES

1. **Whitman G.J., Khan M.A.** Unusual occurrence of ankylosing spondylitis and multiple sclerosis in a black patient, *Cleve Clin J Med*. 1989 Nov-Dec; 56(8):819-22
2. **Mignarri A., Dotti M.T., Battisti C., Vallone I., Federico A.** Occurrence of ankylosing spondylitis and multiple sclerosis-like syndrome in a HLA-B27 positive patient. *Neurol Sci*. 2009 Aug; 30(4):329-32. doi: 10.1007/s10072-009-0092-0. Epub 2009 May 15.
3. **Tan F.U., Tellioğlu S., Aydin G., Erdemoğlu A.K., Keleş.** Ankylosing spondylitis and multiple sclerosis in an HLA-B27 negative patient, *Acta Neurol Belg*. 2004 Dec; 104(4):169-72.
4. **N. Mohan, E.T. Edwards, T.R. Cupps et al.** Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides, *Arthritis & Rheumatism,* vol. 44, no. 12, pp. 2862-2869, 2001
5. **T. Ruiz-Jimeno, A. Carvajal, C. Mata, and E. Aurrecoechea.** Demyelinating disease in a patient with psoriatic arthritis and family history of multiple sclerosis treated with infliximab, *Journal of Rheumatology*, vol. 33, no. 7, pp. 1457-1458, 2006.
6. **M. Gomez-Gallego, J. Meca-Lallana, and A. Fernandez-Barreiro.** Multiple sclerosis onset during etanercept treatment, *European Neurology*, vol. 59, no. 1-2, pp. 91-93, 2007.

7. **E. Andreadou, E. Kemanetzoglou, Ch. Brokalaki, M.E.** Evangelopoulos, C. Kilidireas, A. Rombos, and E. Stamboulis Demyelinating Disease following Anti-TNFa Treatment: A Causal or Coincidental Association? Report of Four Cases and Review of the Literature *Case Reports in Neurological Medicine*, Volume 2013 (2013), Article ID 671935, 9 pages, dx.doi.org/10.1155/2013/671935)
8. **Hanrahan P.S., Russell A.S., McLean D.R.** Ankylosing spondylitis and multiple sclerosis: an apparent association? *J Rheumatol*. 1988 Oct; 15(10):1512-4.
9. **Brown M.A.** Genetics of ankylosing spondylitis. *Curr Opin Rheumatol*. 2010 Mar;22(2):126-32.
10. **Reveille J.D.** The genetic basis of spondyloarthritis. *Ann Rheum Dis*. 2011 Mar; 70 Suppl 1:i44-50
11. **Compston A., Coles A.** (October 2008). Multiple sclerosis. *Lancet* 372 (9648): 1502-17. doi:10.1016/S0140-6736(08)61620-7
12. **Lublin F.D., Reingold S.C.** (April 1996). Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology* 46 (4): 907-11.doi:10.1212/WNL.46.4.907
13. **Tsang B.K., Macdonell R.** (December 2011). Multiple sclerosis-diagnosis, management and prognosis. *Australian family physician* 40 (12): 948-55.
14. **Colombo M.R.** *De Re Anatomica Venice*, 1559
15. **Connor B.** Lettre écrite à Monsieur le chevalier Guillaume de Waldegrave, premier medicin de sa Majeste Britanniue. Paris, 1693:17.
16. **Strümpell A.** Bemerkungen über chronisch-ankylosierende Entzündung der Wirbelsoule und der Huftergelenks. *Deutsch Nervenheilk* 1897; 11:338-42.
17. **Marie P.** Sur la spondylose rhizomelique. *Rev Medecine* 1898; 18:285-315.
18. **Forestier J.** Gilbert Scott memorial oration. Ankylosing spondylitis at the beginning of the century. *Rheumatism* (Journal of the Charterhouse Rheumatism Clinic) 1964; 20:28-53.
19. **Moll J.M., Haslock I., Macrae I.F., Wright V.** Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behçet's syndrome. *Medicine* (Baltimore) 1974; 53:343-64
20. **Wright V., Moll J.M.H., eds**. Seronegative polyarthritis. Amsterdam: North Holland Publishing; 1976.
21. **Holmøy T.** A Norse contribution to the history of neurological diseases. *Eur. Neurol*. (2006)55 (1): 57-8
22. **Pearce J.M.** Historical descriptions of multiple sclerosis. *Eur. Neurol*. (2005) 54(1): 49-53
23. **Clanet M.** Jean-Martin Charcot. 1825 to 1893 (PDF). *Int MS J* (June 2008) 15(2): 59-61.
24. **Braun J., Bollow M., Remlinger G., et al.** Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998; 41:58-67
25. **Ball E.J., Khan M.A.** HLA-B27 polymorphism. *Joint Bone Spine* 2001; 68:378-82
26. **Gonzalez-Roces S., Alvarez M.V., Gonzalez S., Dieye A., Makni H., Woodfield D.G., et al.** HLA-B27 polymorphism and worldwide susceptibility to ankylosing spondylitis. *Tissue Antigens* 1997; 49:116-23.
27. **Pugliatti M., Sotgiu S., Rosati G.** (July 2002). The worldwide prevalence of multiple sclerosis. *Clin Neurol Neurosurg* 104 (3): 182-91
28. **Gourraud P.A., Harbo H.F., Hauser S.L., Baranzini S.E.** The genetics of multiple sclerosis: an up-to-date review, *Immunol Rev*. 2012 Jul; 248(1):87-103.
29. **Sieper J., Braun J., Kingsley G.** Report on the fourth International Workshop on Reactive Arthritis. *Arthritis Rheum* 2000:43:720-34.
30. **Duchmann R., May E., Heike M., Knolle P., Neurath M,. Meyer zum Buschenfelde K.H.** T cell specificity and cross reactivity towards enterobacteria, bacteroides, bifidobacteriium, and antigens from resident intestinal flora in humans. *Gut* 1999; 44:774-5.
31. **Ascherio A., Munger K.L.** (June 2007). Environmental risk factors for multiple sclerosis. Part II: Noninfectious factors. *Annals of Neurology* 61 (6): 504-13
32. **Gilden D.H.** Infectious causes of multiple sclerosis. *The Lancet Neurology,* March 2005 4 (3): 195–202
33. **Milo R., Kahana E.** Multiple sclerosis: geoepidemiology, genetics and the environment. *Autoimmun Rev* (March 2010)9 (5): A387-94
34. **Alonso A., Hernán M.A.** (July 2008). Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology 71* (2): 129-35.
35. **Marrie R.A.** Environmental risk factors in multiple sclerosis aetiology. *Lancet Neurol* (December 2004) 3 (12): 709-18
36. **Spitsin S., Koprowski H.** Role of uric acid in multiple sclerosis. *Curr. Top. Microbiol. Immunol*. (2008) 318: 325-42
37. **M. Rudwaleita, S. Siegerta, Z. Yinb, J. Eicka, A .Thielb, A. Radbruchb, J. Sieperc, J. Brauna.** Low T cell production of TNFα and IFNγ in ankylosing spondylitis: its relation to HLA-B27 and influence of the TNF-308 gene polymorphism. *Ann Rheum Dis* 2001; 60:36-42 doi:10.1136/ard.60.1.36
38. **Kurt Redlich, Birgit Görtz, Silvia Hayer, Jochen Zwerina, George Kollias, Günter Steiner, Josef S. Smolen, Georg Schett.** Overexpression of tumor necrosis factor causes bilateral sacroiliitis *Arthritis Rheum*. 2004 Mar; 50(3):1001-5.
39. **Paul Bowness, Anna Ridley, Jacqueline Shaw, Antoni T. Chan, Isabel Wong-Baeza, Myles Fleming, Fraser Cummings, Andrew McMichael* and Simon Kollnberger.** Th17 Cells Expressing KIR3DL2+ and Responsive to HLA-B27 Homodimers Are Increased in Ankylosing Spondylitis *J. Immunol*. February 15, 2011 vol. 186 no. 4 2672-2680
40. **Sieper J., Braun J.,** (1995) Pathogenesis of spondylarthropathies. *Arthritis Rheum* 38:1547-1554.
41. **Granfors K., Merilahti-Palo R., Luukkainen R., Mottonen T., Lahesmaa R., Probst P., et al.** (1998) Persistence of yersinia antigens in peripheral blood cells from patients with Yersinia enterocolitica O:3 infection with or without reactive arthritis. *Arthritis Rheum*
42. **Erlacher L., McCartney J., Piek E., ten Dijke P., Yanagishita M., Oppermann H., et al.** (1998) Cartilage-derived morphogenetic proteins and osteogenic protein-1 differentially regulate osteogenesis. *J Bone Miner Res* 13:383-392.
43. **Braun J., Bollow M., Eggens U., Koenig H., Distler A., Sieper J., et al.** (1994) Use of dynamic magnetic resonance imaging with fast imaging in the detection of early and advanced sacroiliitis in spondylarthropathy patients. *Arthritis Rheum* 37:1039-1045.
44. **Francois R.J., Gardner D.L., Degrave E.J., Bywaters E.G.** Histopathologic evidence that sacroiliitis in ankylosing spondylitis is not merely enthesitis. *Arthritis Rheum* 2000; 43:2011-24.
45. **Thomas J.T., Lin K., Nandedkar M., Camargo M., Cervenka J., Luyten F.P.** (1996) A human chondrodysplasia due to a mutation in a TGF-beta superfamily member. *Nat Genet* 12:315-317.
46. **Maerker-Hermann E., Fassbender H.G., Kessler S., Thomssen H., Meyer-zum-Büschenfelde K.H., Blessing M.** (1997) Transgenic mice with an epidermal overexpression of bone morphogenic protein-6 present with psoriatic skin lesions and osteoarthropathy [abstract]. *Arthritis Rheum* 40:S261.
47. **Ciccarell O., Barkhof F., Bodin B.** Of multiple sclerosis: insights from molecular and metabolic imaging, *Lancet Neurol* 2014; 13: 807-22
48. **Ellwardt E., Zipp F.** Molecular mechanisms linking neuroinflammation and neurodegeneration in MS, *Exp. Neurol.* (2014),
49. **Rawji K.S., Yong V.W.,** 2013. The benefits and detriments of macrophages/microglia in models of multiple sclerosis. *Clin. Dev. Immunol.* 2013, 13.
50. **Krumbholz M., Derfuss T., Hohlfeld R., Meinl E.** B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat Rev Neurol* 2012; 8: 613-23.
51. **Malviya G., Anzola K.L., Podestà E., et al.** (99m) Tc-labeled rituximab for imaging B lymphocyte infi ltration in infl ammatory autoimmune disease patients. *Mol Imaging Biol* 2012; 14: 637-46.
52. **Venters H.D., Dantzer R., Kelley K.W.,** 2000. A new concept in neurodegeneration: TNFα is a silencer of survival signals. *Trends Neurosci*. 23, 175-180.
53. **Mizuno T., Zhang, G., Takeuchi.** Interferon-γ directly induces neurotoxicity through a neuronspecific, calcium-permeable complex of IFN-γ receptor and AMPA GluR1 receptor. *FASEB J*. 22, 1797-1806.
54. **Giuliani F., Goodyer, C.G., Antel J.P., Yong V.W.,** 2003. Vulnerability of human neurons to T cell-mediated cytotoxicity. *J. Immunol.* 171, 368-379.
55. **Raivich G., Banati R.,** 2004. Brain microglia and blood-derived macrophages: molecular profiles and functional roles in multiple sclerosis and animal models of autoimmune demyelinating disease. *Brain Res*. Rev. 46, 261-281.

56. **Waxman S.G.** Axonal conduction and injury in multiple sclerosis: the role of sodium channels. *Nat. Rev. Neurosci*. 2006. 7, 932-941.
57. **Vergo S., Craner M.J., Etzensperger R., Attfield K., Friese M.A., Newcombe J., Esiri M., Fugger L.,** 2011. Acid-sensing ion channel 1 is involved in both axonal injury and demyelination in multiple sclerosis and its animal model. *Brain* 134, 571-584.
58. **McAteer M.A., Sibson N.R., von Zur Muhlen C., et al.** In vivo magnetic resonance imaging of acute brain inflammation using microparticles of iron oxide. *Nat Med* 2007; 13: 1253-58.
59. **Pitt D., Werner P., Raine C.S.** Glutamate excitotoxicity in a model of multiple sclerosis. *Nat. Med.* 2000 6, 67-70.
60. **Zambonin J.L., Zhao C., Ohno N., Campbell G.R., Engeham S., Ziabreva I., Schwarz N., Lee S.E., Frischer J.M., Turnbull D.M., Trapp B.D., Lassmann H., Franklin R.J.M., Mahad D.J.,** 2011. Increased mitochondrial content in remyelinated axons: implications for multiple sclerosis. *Brain* 134, 1901-1913.
61. **Lavisse S., Guillermier M., Hérard A.S., et al.** Reactive astrocytes overexpress TSPO and are detected by TSPO positron emission tomography imaging. *J Neurosci* 2012; 32: 10809-18.
62. **Braun J., Sieper J.** Inception cohorts for spondyloarthropathies. *Z Rheumatol* 2000; 59:117-21.
63. **Zink A., Braun J., Listing J., Wollenhaupt J.** Disability and handicap in rheumatoid arthritis and ankylosing spondylitis – results from the German rheumatological database. *J Rheumato*l 2000; 27:613-22
64. **Feldtkeller E.** Age at disease onset and delayed diagnosis of spondyloarthropathies. *Z Rheumato* l1999; 58:21-30.
65. **McBryde A.M., McCollum D.E.** Ankylosing spondylitis in women. The disease and its prognosis. *N C Med J* 1973; 34:34-7.
66. **Braunstein E.M., Martel W., Moidel R.** Ankylosing spondylitis in men and women: a clinical and radiographic comparison. *Radiology* 1982; 144:91-4.
67. **Carette S., Graham D., Little H., Rubenstein J., Rosen P.** The natural disease course of ankylosing spondylitis. *Arthritis Rheum* 1983; 26:186-90
68. **Gunnstein Bakland, Jan Tore Gran, Johannes C. Nossent.** Increased mortality in ankylosing spondylitis is related to disease activity, *Ann Rheum Dis* 2011; 70:1921-1925 doi:10.1136/ard.2011.151191
69. **Amor B., Santos R.S., Nahal R., Listrat V., Dougados M.** Predictive factors for the longterm outcome of spondyloarthropathies. *J Rheumatol* 1994; 21:1883-7.
70. **Radford E.P., Doll R., Smith P.G.** (September 1977). Mortality among patients with ankylosing spondylitis not given X-ray therapy. *N. Engl. J. Med*. 297 (11): 572-6.
71. **Hassan-Smith G., Douglas M.R.** (October 2011). Epidemiology and diagnosis of multiple sclerosis. *British journal of hospital medicine* (London, England: 2005) 72 (10): M146-51
72. **Brophy S., Calin A.** Definition of disease flare in ankylosing spondylitis: the patients' perspective. *J. Rheumatol.* 29 (5), 954-958 (2002)
73. **Cooksey R.** et al. (2010, May). Frequency and characteristics of disease flares in ankylosing spondylitis. *Rheumatology* (Oxford), 49(5), 929-932.
74. **Miller D., Barkhof F., Montalban X., Thompson A., Filippi M.** (May 2005). Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol* 4 (5): 281-8.
75. **El Maghraoui A.** Extra-articular manifestations of ankylosing spondylitis: prevalence, *Eur J Intern Med*. 2011 Dec; 22(6):554-60. Epub 2011 Jul 13.
76. **Martin Tammy M., Evans David M., Danoy Patrick, Smith Justine R., Ward, Michael M., Weisman Michael H., et al.** Genomewide Scan in Acute Anterior Uveitis: Similarities and Differences with Genes Associated with Ankylosing Spondylitis [abstract]. *Arthritis Rheum* 2009; 60 Suppl 10 :1231, DOI: 10.1002/art.26305
77. **Pillay N., Hunter T.** Delayed evoked potentials in patients with ankylosing spondylitis. *J Rheumatol*. 1986 Feb; 13(1):137-41.
78. **Eman M. Khedr, Sonia M. Rashad, Sherifa A. Hamed, Fatma El-Zharaa, Abdel Karim H. Abdalla.** Neurological complications of ankylosing spondylitis: neurophysiological assessment, *Rheumatology International*, June 2009, Volume 29, Issue 9, pp 1031-1040.
79. **Bermel R.A., Balcer L.J.** Optic neuritis and the evaluation of visual impairment in multiple sclerosis, *Continuum (Minneap Minn*). 2013 Aug; 19(4 Multiple Sclerosis):1074-86. doi: 10.1212/01. CON.0000433282.00221.7e.
80. **Baraliakos X., Heldmann F., Callhoff J., et al.** Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. *Ann Rheum Dis* 2013. doi:10.1136/annrheumdis-2013-203425.
81. **Chiowchanwisawakit P., Lambert R.G., Conner-Spady B., et al.** Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. *Arthritis Rheum 2011*; 63:2215-25.
82. **Rudwaleit M., van der Heijde D., Landewé R., et al.** The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68:777.
83. **Gronseth G.S., Ashman E.J.** Practice parameter: the usefulness of evoked potentials in identifying clinically silent lesions in patients with suspected multiple sclerosis (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 54 (May 2000 (9): 1720-5.
84. **Braun J., van den Berg R., Baraliakos X., et al.** 2010 update of the ASAS/EULAR recommendations for the management of ankylosing *Ann Rheum Dis*. 2011 Jun; 70(6):896-904.
85. **Brandt J., Haibel H., Cornely D., et al.** Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. *Arthritis Rheum* 2000; 43:1346-52.
86. **M. Ramos-Casals, Roberto-Perez-Alvarez, C. Diaz-Lagares, M.J. Cuadrado, M.A. Khamashta.** Autoimmune diseases induced by biological agents: a double-edged sword? *Autoimmunity Reviews*, vol. 9, no. 3, pp. 188-193, 2010.)
87. **K. Nozaki, R.M. Silver, D.E. Stickler et al.** Neurological deficits during treatment with tumor necrosis factor-alpha antagonists. *The American Journal of the Medical Sciences*, vol. 342, no. 5, pp. 352-355, 2011.
88. **Mejico L.J.** Infliximab-associated retrobulbar optic neuritis, *Archives of Ophthalmology,* vol. 122, no. 5, pp. 793-794, 2004.
89. **Faillace C., J.R. de Almeida, J.F. de Carvalho.** Optic neuritis after infliximab therapy, *Rheumatology International*, vol. 33, no. 4, pp. 1101-1103, 2013.
90. **F. Atzeni, P. Sarzi-Puttini, D. Dell' Acqua et al.** Adalimumab clinical efficacy is associated with rheumatoid factor and anti-cyclic citrullinated peptide antibody titer reduction: a one-year prospective study, *Arthritis Research & Therapy*, vol. 8, no. 1, article R3, 2006.
91. **P. Lozeron, C. Denier, C. Lacroix, D. Adams.** Long-term course of demyelinating neuropathies occurring during tumor necrosis factor-a-blocker therapy, *Archives of Neurology*, vol. 66, no. 4, pp. 490-497, 2009.
92. **I.S.J. Shin, A.N. Baer, H.J. Kwon, E.J.** Papadopoulos, and J.N. Siegel. Guillain-Barré and Miller Fisher syndromes occurring with tumor necrosis factor α antagonist therapy, *Arthritis and Rheumatism*, vol. 54, no. 5, pp. 1429-1434, 2006.
93. **Saidha S., Eckstein C., Calabresi P.A.** New and emerging disease modifying therapies for multiple sclerosis. *Annals of the New York Academy of Sciences* (January 2012)1247: 117-37.
94. **Serena Ruggieri, Carla Tortorella, Claudio Gasperini.** Pharmacology and clinical efficacy of dimethyl fumarate (BG-12) for treatment of relapsing – remitting multiple sclerosis, *Therapeutics and Clinical Risk Management* 2014:10 229-239.
95. **Hassan-Smith G., Douglas M.R.** Management and prognosis of multiple sclerosis. *British journal of hospital medicine* (November 2011) (London, England : 2005) 72 (11): M174-6.
96. **Bates D.** Treatment effects of immunomodulatory therapies at different stages of multiple sclerosis in short-term trials. *Neurology* 76 (January 2011) (1 Suppl 1): S14-25.
97. **Burton J.M., O'Connor P.W., Hohol M., Beyene J.** Oral versus intravenous steroids for treatment of relapses in multiple sclerosis. *Cochrane* Database of Systematic Reviews (12): CD006921 (12 December 2012) (Orig. rev.).
98. **Haibel H., Fendler C., Listing J., et al.** Efficacy of oral prednisolone in active ankylosing spondylitis: results of a double-blind, randomised, placebo-controlled short-term trial. *Ann Rheum Dis* 2014; 73:243-6.